Claims

1. A method for identifying a potential modulator compound for ErbB2 which method comprises:

(a) providing a three-dimensional structure of

(i) amino acids 1-509 of ErbB2 polypeptide having the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I; or

(ii) a subset of said amino acids having a corresponding subset of the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I;

(b) providing the three-dimensional structure of a candidate compound;

(c) assessing the stereochemical complementarity between the three-dimensional structure of step (b) and a region of the three-dimensional structure of step (a); and

(d) selecting a compound on the basis of the stereochemical complementarity.

2. A method as claimed in claim 1, which further comprises:

(e) synthesising or obtaining a candidate compound assessed in step (c) as possessing stereochemical complementarity with a topographical region of the three-dimensional structure of step (a);

(f) determining the ability of the candidate compound to interact with and/or modulate the activity of ErbB2.

3. A method as claimed in claim 1 or claim 2, wherein the subset of amino acids is selected from at least one of the CR1 domain, the potential CR1 loop docking site between the L1, CR1 and L2 domains, the CR1-L2 hinge region, the regions of the L1 and L2 domains that contact each other in a closed conformation.

4. A method as claimed in any one of the preceding claims, wherein the subset of amino acids defines at least a part of the heterodimerisation surface with another member of the EGF receptor family.

5. A method as claimed in claim 4, wherein the member of the EGF receptor family is selected from the group consisting of ErbB1 (EGF receptor), ErbB3 and ErbB4.

6. A method as claimed in claim 4 or 5, wherein the heterodimerisation surface includes at least one of (i) the N-terminal end of the CR1 domain, (ii) the CR1 domain dimerisation loop and adjacent residues and (iii) the C-terminal end of the CR1 domain.

7. A method according to claim 6, wherein the surface comprises at least one of residues selected from 200-203, 210-213, 216-218, 225-230, 247-268, 244-246, 285-289) and 294-319.

8. A method as claimed in claim 3, wherein the subset defines the CR1 loop docking site.

9. A method as claimed in claim 8, wherein the docking site comprises at least one of the following ErbB2 residues: Gln 36, Gln 60, Arg 82, Thr 84, Gln 85, Phe 237, Thr 269, Phe 270, Gly 271, Ala 272, Tyr 282, Thr 285, Gly 288, Ser 289, Cys 290, Thr 291, Leu 292, Val 293, Cys 294, Pro 295 and Cys 310.

10. A method as claimed in any one of the preceding claims wherein the method is performed *in silico*.

11. A method as claimed in claim 10, wherein the candidate compound is selected from a real compound, a virtual compound or a combination thereof.

12. A method as claimed in claim 10 or 11, wherein the compound is in a library with at least one other candidate compound.

13. A method as claimed in any one of claims 10 to 12, wherein the method is used for targeted screening.

14. A method as claimed in any one of claims 10 to 12, wherein the library comprises an array of maximally diverse compounds.

15. A method of modulating ErbB2, the method comprising contacting the receptor with a compound that matches a region selected from at least one of the CR1 domain, the potential CR1 loop docking site between the L1, CR1 and L2 domains, the CR1-L2 hinge region, and the regions of the L1 and L2 domains that contact each other in a closed conformation.

16. A method as claimed in claim 15, wherein the region is a heterodimerisation surface of the receptor with another member of the EGF receptor family.

17. A method according to claim 16, wherein the other member of the EGF receptor family is selected from the group consisting of ErbB1 (EGF receptor), ErbB3 and ErbB4.

18. A method as claimed in claim 16 or 17, wherein the heterodimerisation surface includes at least one of (i) the N-terminal end of the CR1 domain, (ii) the CR1 domain dimerisation loop and adjacent residues and (iii) the C-terminal end of the CR1 domain.

19. A method according to claim 18, wherein the surface comprises at least one of residues selected from 200-203, 210-213, 216-218, 225-230, 247-268, 244-246, 285-289) and 294-319.

20. A method as claimed in claim 16 or claim 17, wherein the region is the CR1 loop docking site.

21. A method as claimed in claim 20, wherein the region comprises at least one of the following ErbB2 residues: Gln 36, Gln 60, Arg 82, Thr 84, Gln 85, Phe 237, Thr 269, Phe 270, Gly 271, Ala 272, Tyr 282, Thr 285, Gly 288, Ser 289, Cys 290, Thr 291, Leu 292, Val 293, Cys 294, Pro 295 and Cys 310.

22. A method as claimed in any one of claims 15 to 21, wherein the molecule is a small molecule modulator.

23. A method as claimed in claim 22, wherein the small molecule is identified by the method of claim 1.

24. A method according to any one of claims 15 to 21, wherein the molecule is an antibody.

25. A computer-based method of identifying a candidate modulator of ErbB2, which method comprises fitting the structure of

(a) amino acids 1-509 of ErbB2 polypeptide having the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I; or

(b) a subset of said amino acids having a corresponding subset of the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I;

to the structure of a candidate modulator molecule.

26. A computer-assisted method for identifying candidate compounds able to interact with ErbB2 and thereby modulate an activity mediated by the receptor, using a programmed computer comprising a processor, an input device, and an output device, which method comprises the steps of:

(a) entering into the programmed computer, through the input device, data comprising the atomic coordinates of amino acids 1-509 of ErbB2 as shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I, or a subset of said coordinates;

(b) generating, using computer methods, a set of atomic coordinates of a structure that possesses stereochemical complementarity to the atomic coordinates entered in step (a), thereby generating a criteria data set;

(c) comparing, using the processor, the criteria data set to a computer database of chemical structures;

(d) selecting from the database, using computer methods, chemical structures which are similar to a portion of said criteria data set; and

(e) outputting, to the output device, the selected chemical structures which are complementary to or similar to a portion of the criteria data set.

27. A method for evaluating the ability of a candidate modulator to interact with ErbB2, said method comprising the steps of:

(a) providing a computer model of at least one region of ErbB2 using structure coordinates wherein the root mean square deviation between said structure coordinates and the structure coordinates of amino acids 1-509 of ErbB2 as set forth in Appendix I is not more than 1.5 Å;

(b) employing computational means to perform a fitting operation between the chemical entity and said computer model of the binding surface; and

(c) analysing the results of said fitting operation to quantify the association between the chemical entity and the binding surface model.

28. A computer system for identifying one or more candidate modulators of ErbB2 , the system containing data representing the structure of

(a) amino acids 1-509 of ErbB2 polypeptide having the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I; or

(b) a subset of said amino acids having a corresponding subset of the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I.

29. A computer for producing a three-dimensional representation of a molecule or molecular complex, wherein the computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein the machine readable data comprises (i) the atomic coordinates of amino acids 1-509 of ErbB2 polypeptide as shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I; or (ii) the atomic coordinates of a subset of said amino acids having a corresponding subset of the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I;

(b) a working memory for storing instructions for processing the machine-readable data;

(c) a central-processing unit coupled to the working memory and to the machine-readable data storage medium, for processing the machine-readable data into the three dimensional representation; and

(d) an output hardware coupled to the central processing unit, for receiving the three-dimensional representation.

30. A computer readable media having recorded thereon data representing a model and/or the atomic coordinates of a ErbB2 crystal.

31. A computer readable media having recorded thereon coordinate data according to Appendix I, or a subset thereof, where said coordinate data define a three dimensional structure of amino acids 1-509 of ErbB2 polypeptide or a subset of said amino acids, or coordinate data having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinate according to Appendix I, or a subset thereof.

32. A crystal of ErbB2 polypeptide.

33. A crystal of ErbB2 polypeptide having a space group $P2_12_12_1$ with unit cell dimensions of a=75.96 Å, b=82.24 Å, and c=110.06 Å, with up to about 1% variation in any cell dimension

34. A crystalline composition comprising a crystal of ErbB2.

35. A method of using molecular replacement to obtain structural information about a molecule or a molecular complex of unknown structure, comprising the steps of:

(a) crystallising said molecule or molecular complex;

(b) generating an X-ray diffraction pattern from said crystallized molecule or molecular complex;

(c) applying at least a portion of the structure coordinates set forth in Appendix I, or structure coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the structure coordinates set forth in Appendix I, to the X-ray diffraction

pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.

36. A method according to claim 35 wherein the molecule of unknown structure is ErbB2 or variant thereof.

37. A method according to claim 36 wherein the molecular complex of unknown structure is a complex of ErbB2 and an EGF receptor.

38. A method according to claim 37 wherein the molecular complex of unknown structure is a complex of ErbB2, an ErbB1, ErbB3 or ErbB4 receptor and a ligand or candidate ligand.

39. A method for preventing or treating a disease associated with signaling by ErbB2 which method comprises administering to a subject in need thereof a compound identified by the method of any one of claims 1 to 27.

40. A pharmaceutical composition comprising a compound identified by the method of any one of claims 1 to 27.

41. A method for preparing a pharmaceutical composition for treating diseases associated with aberrant ErbB2 signalling, the method comprising:

(a) providing a three-dimensional structure of

(i) amino acids 1-509 of ErbB2 polypeptide having the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I; or

(ii) a subset of said amino acids having a corresponding subset of the atomic coordinates shown in Appendix I, or atomic coordinates having a root mean square deviation of backbone atoms of not more than 1.5Å when superimposed on the corresponding backbone atoms described by the atomic coordinates shown in Appendix I;

(b) providing the three-dimensional structure of a candidate compound;

(c) assessing the stereochemical complementarity between the three-dimensional structure of step (b) and a region of the three-dimensional structure of step (a); and

(d) selecting a compound on the basis of the stereochemical complementarity;

(e) synthesising or obtaining a candidate compound assessed in step (c) as possessing stereochemical complementarity with the three-dimensional structure of step (a);

(f) determining the ability of the candidate compound to interact with and/or modulate the activity of ErbB2; and

(g) incorporating the compound into a pharmaceutical composition.

42. A method of preventing or treating a disease associated with signalling by ErbB2 which method comprises administering to a subject in need thereof a composition according to claim 40.

43. An antibody that binds to ErbB2, the antibody being directed against at least one of the N-terminal end of the CR1 domain, the CR1 domain dimerisation loop and adjacent residues and the C-terminal end of the CR1 domain.

44. An antibody as claimed in claim 43, the antibody being directed against a structure defined by (i) ErbB2 amino acid residues 200-203, (ii) ErbB2 amino acid residues 210-213, (iii) ErbB2 amino acid residues 216-218, (iv) ErbB2 amino acid residues 225-230, (v) ErbB2 amino acid residues 247-268 or a subset thereof; (vi) ErbB2 amino acid residues 244-246, (vii) ErbB2 amino acid residues 285-289, or (viii) ErbB2 amino acid residues 294-319 or a subset thereof.

45. An isolated conformationally constrained peptide or peptidomimetic consisting essentially of (i) ErbB2 amino acid residues 200-203, (ii) ErbB2 amino acid residues 210-213, (iii) ErbB2 amino acid residues 216-218, (iv) ErbB2 amino acid residues 225-230, (v) ErbB2 amino acid residues 247-268 or a subset thereof; (vi) ErbB2 amino acid residues 244-246, (vii) ErbB2 amino acid residues 285-289, or (viii) ErbB2 amino acid residues 294-319 or a subset thereof.

46. An *in vitro* assay for identifying a potential modulator compound for ErbB2 the method comprising contacting a candidate compound with a CR1 domain dimerisation loop or fragment thereof and determining whether the compound binds to the dimerisation loop or fragment thereof.